Fu B, et al., J Addict Addictv Disord 2022, 9: 076
DOI: 10.24966/AAD-7276/100076

HSOA Journal of Addiction & Addictive Disorders

Short review

Dorsal Raphe Nucleus 5-HT Neurons: A New Target for Rewarding Regulation and Drug Addiction

Bo Fu[1]*, Xiaoming Wang[2]*, Ming Huang[3], Zeqi Li[1], Chang Lu[4] and Hui Peng[1]

[1]*Laboratory of Occupational Medicine, Tianjin Institute of Environmental and Occupational medicine, Tianjin, China*

[2]*Institute of Environment and Operational Medicine, Academy of Military Medical Sciences, Academy of Military Sciences, Tianjin, China*

[3]*School of Basic Medicine and Clinical Pharmacy, China Pharmaceutial University, Nanjing, China*

[4]*Tjanjin University of Traditional Chinese Medicine, Tianjin, China*

Abstract

In current paper, we reviewed the functional mechanisms of Dorsal Raphe Nucleus (DRN) 5-HT neurons in rewarding regulation and drug addiction in the level of molecular, neuron and neural circuits. Furtherly, we prospected that the DRN 5-HT neurons might be a new drug target for addiction treatment in future.

Introduction

It has been proposed that reward was divided into two types, including the pleasure brought by the enjoyment of emotion and motivation made by motivating individuals to obtain the reward. According to the classification of reward attributes, it can be divided into natural reward and drug reward. Natural rewards usually refer to water, food, sex and social interaction, while drug rewards usually induced by drugs such as morphine and cocaine. The mechanisms of rewarding effect are still complex and controversial. Traditional views suggest that the limbic dopamine system is the key to inducing the reward and leading to the addictive behaviors. Take morphine for example. Morphine interacts with m-Opioid Receptors (MORs) expressed in the Ventral Tegmental Area (VTA) γ-Aminobutyric acid (GABAergic) neurons and relieves the local inhibitory tone leading to reduced inhibition of the VTA dopaminergic neurons [1]. This in turn releases Dopamine (DA) in the Nucleus Accumbens (NAc) [2], which is considered a reward center for reward [3].

However, the long-term use of morphine can lead to drug abuse and addiction. Morphine addiction is characterized by negative physical and emotional feelings when the drug is terminated and causes drug-craving in mental functions and drug-seeking in behavioral changes [4]. Conversely, knockout of the dopamine transporter genetically does not inhibit the rewarding properties in the model of self-administration and Conditioned Place Preference (CPP) [5,6]. In addition, morphine addiction is still observed in dopamine-deficient mice [7], indicating that additional mechanisms of morphine addiction existed outside the dopaminergic system.

5-HT and Reward Regulation

5-Hydroxytryptamine (5-HT), is an important inhibitory neurotransmitter in the brain, which is synthesized and secreted by Dorsal Raphe Nucleus (DRN) 5-HT neurons. DRN 5-HT neurons can form synaptic connections with almost whole brain nucleus and project to the forebrain and limbic areas like Medial Prefrontal Cortex (mPFC), NAc, amygdala, lateral habenula nucleus and VTA to form complex neural circuits [8]. Clinical studies have shown that 5-HT reuptake inhibition like fluoxetine and ciprotidran can relieve anhedonia in depression patients, suggesting that 5-HT is closely associated with rewarding effect. Genetically deleted both dopamine and 5-HT transporter in mice inhibited the cocaine CPP [9], indicating that 5-HT might play a role in reward regulation beside dopamine. Recently, several researches have reported that motivational, reinforcement and reward waiting behaviors could be induced by activating of DRN 5-HT neurons optogenetically in mice [10-12]. Our group showed that optogenetically activated 5-HT neurons in the DRN to mediate real-time CPP, suggesting that rewarding effect was led by activation of 5-HT neurons [13]. Other work in our group has shown that long-term fluoxetine use can induce significant conditional place preference (not published). These results suggest that 5-HT plays a more important role in reward regulation.

However, there is some controversy about the reward regulation of DRN 5-HT neurons because of 5-HT can show reward and punishment through different neural projections. This means DR 5-HT neurons can encode reward and aversion [14].

5-HT and Drug Addiction

It is generally believed that the addictive drugs mediated the dysfunction of mesolimbic dopaminergic system are the reasons of addiction. In neuroanatomy, DRN 5-HT neurons interactions with the mesolimbic dopaminergic system and regulate the reward effect of addictive drugs such as morphine [15]. A recently study reported

***Corresponding authors:** Bo Fu, Laboratory of occupational medicine, Tianjin Institute of Environmental and Occupational medicine, Tianjin, 300050, China, Tel: +86 02284655056; E-mail: faith_fubo@outlook.com

Xiaoming Wang, Institute of environment and operational medicine, Academy of Military Medical Sciences, Academy of Military Sciences, Tianjin, 300050, China, E-mail: sisuo55123@sina.com

Citation: Fu B, Wang X, Huang M, Li Z, Lu C (2022) Dorsal Raphe Nucleus 5-HT Neurons: A New Target for Rewarding Regulation and Drug Addiction. J Addict Addictv Disord 9: 076.

Received: December 21, 2021; **Accepted:** December 31, 2021; **Published:** January 07, 2022

that the inhibitory pathway of GABAergic neurons in the cephalic region of the VTA project to the DRN 5-HT neurons played an important role in morphine addiction, and optogenetically activated this inhibitory pathway to block the morphine rewarding effect and rescued the mental dependence [15]. By activating this GABAergic inhibitory pathway projected to the DRN, the inhibitory neurotransmitter GABA was released locally in the DRN, and then inhibited the activity of 5-HT neurons. Our study also found that morphine could increase DRN 5-HT neurons firing rate *in vivo*, and inhibited 5-HT neurons after morphine administration by optogenetic blocked morphine-induced CPP [13].

5-HT receptor is closely related to reward regulation and drug addiction. 5-HT receptors can be divided into 7 families according to their function, structure and signal transduction characteristics, including 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6 and 5-HT7. Except for 5-HT3 receptor conjugated with cationic channel type receptor, the other receptors were G protein conjugated receptors [16]. Many researched reported that 5-HT2 receptor family might be a key factor in drug addiction. The selective 5-HT2C receptor agonist Ro60-0175 did not affect methamphetamine-induced impulsive behavior at low doses. However, a higher dose of Ro60-0175 and M100907, a selective antagonist of 5-HT2A, can reduce the impulsive behavior of methamphetamine and cocaine [17]. Injection of 5-HT2A receptor antagonist M100907 into mPFC attenuated cue-induced cocaine seeking behavior, but the same dose of M100907 did not affect cocaine self-administration. These results further confirmed the role of 5-HT2A receptor of mPFC in cue-induced cocaine seeking behavior [18]. Systematic injection of 5-HT2C receptor agonist RO60-0175 reduced self-administration of cocaine [19]. The mPFC administered 5-HT2C receptor agonist MK212 in a dose-dependent manner to reduce cocaine ignition and drug-seeking behavior induced by conditioned cues, which was reversed by selective 5-HT2C receptor antagonist SB242084 [20]. Activation of 5-HT2C receptor in VTA leads to a decrease in dopamine level in NAc. Therefore, 5-HT2A /2C receptor may play its role in reducing drug igniting and cue-induced drug seeking behavior. In summery DRN 5-HT neurons will be a new target for the treatment of drug addiction.

Outlook

The DRN 5-HT neurons is believed sensitive to reward and drug addiction, our group presents evidence that morphine regulates DRN 5-HT neurons to induce a rewarding effect and that the DRN 5-HT system participates in chronic morphine-induced CPP [13]. However, further studies are needed to establish the exact role of the DRN 5-HT system on other addictive drug effects that leads to addiction and withdrawal symptoms. The mechanisms including molecular, receptors, synaptic, neurons and even neural circuits should be investigated in the future, and provided more directions to clinical treatment of drug addiction.

References

1. Wise RA, Rompre PP (1989) Brain dopamine and reward. Annu Rev Psychol 40: 191-225.
2. Fields HL, Margolis EB (2015) Understanding opioid reward. Trends Neurosci 38: 217-225.
3. Russo SJ, Nestler EJ (2013) The brain reward circuitry in mood disorders. Nat Rev Neurosci 14: 609-625.
4. Vargas-Perez H, Ting-A-Kee RA, Heinmiller A, Sturgess JE, van der Kooy D (2007) A test of the opponent-process theory of motivation using lesions that selectively block morphine reward. Eur J Neurosci 25: 3713-3718.
5. Rocha BA, Fumagalli F, Gainetdinov RR, Jones SR, Ator R, et al. (1998) Cocaine self-administration in dopamine-transporter knockout mice. Nat Neurosci 1: 132-137.
6. Sora I, Wichems C, Takahashi N, Li XF, Zeng Z, et al. (1998) Cocaine reward models: Conditioned place preference can be established in dopamine- and in serotonin-transporter knockout mice. Proc Natl Acad Sci USA 95: 7699-7704.
7. Hnasko TS, Sotak BN, Palmiter RD (2005) Morphine reward in dopamine-deficient mice. Nature 438: 854-857.
8. Luo M, Zhou J, Liu Z (2015) Reward processing by the dorsal raphe nucleus: 5-HT and beyond. Learn Mem 22: 452-460.
9. Sora I, Hall FS, Andrews AM, Itokawa M, Li XF, et al. (2001) Molecular mechanisms of cocaine reward: combined dopamine and serotonin transporter knockouts eliminate cocaine place preference. Proc Natl Acad Sci USA 98: 5300-5305.
10. Liu Z, Zhou J, Li Y, Hu F, Lu Y, et al. (2014) Dorsal raphe neurons signal reward through 5-HT and glutamate. Neuron 81: 1360-1374.
11. Li Y, Zhong W, Wang D, Feng Q, Liu Z, et al. (2016) Serotonin neurons in the dorsal raphe nucleus encode reward signals. Nature Communications 7: 10503.
12. Miyazaki K, Miyazaki KW, Sivori G, Yamanaka A, Tanaka KF, et al. (2020) Serotonergic projections to the orbitofrontal and medial prefrontal cortices differentially modulate waiting for future rewards. Sci Adv 6: eabc7246.
13. Fu B, Yao JQ, Lu C, Wang B, Li Z, et al. (2022) Dorsal Raphe Nucleus Serotoninergic Neurons Mediate Morphine Rewarding Effect and Conditioned Place Preference. Neuroscience 480: 108-116.
14. Nagai Y, Takayama K, Nishitani N, Andoh C, Koda M, et al. (2020) The Role of Dorsal Raphe Serotonin Neurons in the Balance between Reward and Aversion. Int J Mol Sci 21: 2160.
15. Li Y, Li CY, Xi W, Jin S, Wu ZH, et al. (2019) Rostral and Caudal Ventral Tegmental Area GABAergic Inputs to Different Dorsal Raphe Neurons Participate in Opioid Dependence. Neuron 101: 748-761.
16. Ślifirski G, Król M, Turło J (2021) 5-HT Receptors and the Development of New Antidepressants. Int J Mol Sci 22: 9015.
17. Fletcher PJ, Rizos Z, Noble K, Higgins GA (2011) Impulsive action induced by amphetamine, cocaine and MK801 is reduced by 5-HT(2C) receptor stimulation and 5-HT(2A) receptor blockade. Neuropharmacology 61: 468-477.
18. Katsidoni V, Apazoglou K, Panagis G (2011) Role of serotonin 5-HT2A and 5-HT2C receptors on brain stimulation reward and the reward-facilitating effect of cocaine. Psychopharmacology (Berl) 213: 337-354.
19. Fletcher PJ, Rizos Z, Sinyard J, Tampakeras M, Higgins GA (2008) The 5-HT2C receptor agonist Ro60-0175 reduces cocaine self-administration and reinstatement induced by the stressor yohimbine, and contextual cues. Neuropsychopharmacology 33: 1402-1412.
20. Pentkowski NS, Duke FD, Weber SM, Pockros LA, Teer AP, et al. (2010) Stimulation of medial prefrontal cortex serotonin 2C (5-HT(2C)) receptors attenuates cocaine-seeking behavior. Neuropsychopharmacology 35: 2037-2048.

HERALD

Advances In Industrial Biotechnology | ISSN: 2639-5665

Advances In Microbiology Research | ISSN: 2689-694X

Archives Of Surgery And Surgical Education | ISSN: 2689-3126

Archives Of Urology

Archives Of Zoological Studies | ISSN: 2640-7779

Current Trends Medical And Biological Engineering

International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X

Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276

Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292

Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370

Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594

Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X

Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562

Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608

Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879

Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397

Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751

Journal Of Aquaculture & Fisheries | ISSN: 2576-5523

Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780

Journal Of Biotech Research & Biochemistry

Journal Of Brain & Neuroscience Research

Journal Of Cancer Biology & Treatment | ISSN: 2470-7546

Journal Of Cardiology Study & Research | ISSN: 2640-768X

Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943

Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771

Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844

Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801

Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978

Journal Of Cytology & Tissue Biology | ISSN: 2378-9107

Journal Of Dairy Research & Technology | ISSN: 2688-9315

Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783

Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X

Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798

Journal Of Environmental Science Current Research | ISSN: 2643-5020

Journal Of Food Science & Nutrition | ISSN: 2470-1076

Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X

Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566

Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485

Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662

Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999

Journal Of Hospice & Palliative Medical Care

Journal Of Human Endocrinology | ISSN: 2572-9640

Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654

Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493

Journal Of Light & Laser Current Trends

Journal Of Medicine Study & Research | ISSN: 2639-5657

Journal Of Modern Chemical Sciences

Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044

Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X

Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313

Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400

Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419

Journal Of Obesity & Weight Loss | ISSN: 2473-7372

Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887

Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052

Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X

Journal Of Pathology Clinical & Medical Research

Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649

Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670

Journal Of Plant Science Current Research | ISSN: 2639-3743

Journal Of Practical & Professional Nursing | ISSN: 2639-5681

Journal Of Protein Research & Bioinformatics

Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150

Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177

Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574

Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060

Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284

Journal Of Toxicology Current Research | ISSN: 2639-3735

Journal Of Translational Science And Research

Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193

Journal Of Virology & Antivirals

Sports Medicine And Injury Care Journal | ISSN: 2689-8829

Trends In Anatomy & Physiology | ISSN: 2640-7752